

REMARKS

Applicants would like to thank Examiner Hunt for the courtesy extended to their attorneys, Thomas C. Gallagher, Patrick J. Birde, and Kathryn M. Lumb, in granting an Interview on November 14, 2001. Following a discussion of the outstanding issues, a record of which can be found in the Interview Summary, the Examiner agreed that claims discussed during the Interview would likely obviate section 112, paragraph 2 issues, as well as section 103 obviousness issues. With respect to section 112, paragraph 1 issues, the Examiner indicated that, although epidermal growth factor receptor (EGFR) antagonist is a broad term, a showing of a discrete mechanism of action specific for all EGFR antagonists would be sufficient to enable such a term.

The Claimed Invention

The present invention is directed to methods of treating refractory tumors. (Specification p. 5, ll. 18-20.) The refractory tumors of the newly claimed invention have failed or been resistant to treatment. (Specification p. 5, ll. 22-23.) In the present inventive methods, a human patient is treated by administration of an antagonist of EGFR in combination with an antineoplastic agent, such as a chemotherapeutic agent or radiation. (Specification p. 17, ll. 19-21.)

Amendments

The specification has been amended to correct inadvertent typographical errors and to literally include material that had been incorporated by reference.

Claims 1-35 have been deleted and new claims 36-125 have been added. The new claims have been added to more particularly point out and distinctly claim the present invention.

The amendments to the specification and new claims and abstract are fully supported by the specification as originally filed. Accordingly, no new matter has been added. It should be noted, however, that the new claims recite therapy using an EGFR antagonist in combination with an antineoplastic agent. Claims reciting therapy using an EGFR antagonist alone are being pursued in another continuation application filed November 28, 2001.

Attached hereto are a copy of a version of the amendments with markings to show the changes made and, for the convenience of the Examiner, a copy of the pending claims upon entry of the present amendments.

Outstanding Issues

The present application is a continuation of Application No. 09/374,028. In the parent '028 application, an Office Action dated October 24, 2000, was outstanding. In this Office Action, the Office had issued the following rejections: (i) claims 1-33 were rejected under 35 U.S.C. § 112, ¶ 2 as unclear (ii) claims 1-33 were rejected under 35 U.S.C. § 112, ¶ 1 as not enabled by the specification; and (iii) claims 1-33 were rejected under 35 U.S.C. § 103(a) as obvious over Baselga et al., *Breast Cancer Res.*, 29: 127-138 (1994) alone (claims 1-3, 6-9, and 22-23) or in light of Han et al., *Oncol. Res.*, 9: 581-87 (1997) (claims 1-9 and 22-33) or U.S. Patent No. 4,863,902 (Amagase et al.) (claims 1-3 and 6-33).

Section 112, Second Paragraph Issues

In the Office Action dated October 24, 2000, claims 1-33 were rejected under 35 U.S.C. § 112, ¶ 2 for unclear recitation of "refractory tumor". The new claims specify the refractory tumors of the present invention as having failed or been resistant to treatment, i.e., first line treatment. Accordingly, this rejection is moot and should be withdrawn.

In the Office Action dated October 24, 2000, claims 1-33 were also rejected under 35 U.S.C. § 112, ¶ 2, for unclear recitation of "effective amount". The new claims recite that administration of the EGFR antagonist and the chemotherapeutic agent, or radiation, is effective to inhibit growth of the refractory tumor. Such inhibition is sufficient to prevent or reduce the progression, i.e., growth, invasion and/or metastasis, of the refractory tumor. As such, this rejection is moot and should be withdrawn.

Section 112, First Paragraph Issues

In the Office Action dated October 24, 2000, claims 1-33 were rejected under 35 U.S.C. § 112, ¶ 1 as not enabled by the specification. According to the Office, there is no enablement for treatment of all tumors with all EGFR antagonists either alone or in combination with a chemotherapeutic agent. As discussed during the Examiner Interview, new claims recite that the type of tumor encompassed by the present invention has failed or been resistant to treatment. Furthermore, as discussed previously, claims directed to monotherapy are being pursued in a separate application. It appears that, in light of the Examiner Interview and the new claims, there may be a remaining issue with respect to the scope of the term EGFR antagonist.

An EGFR antagonist, in the context of the present invention, is any substance that inhibits stimulation of EGFR. (Specification p. 7, ll. 3-5.) Binding of a ligand, e.g.,

epidermal growth factor (EGF) or transforming growth factor- α (TGF- α), to an external, extracellular domain of EGFR stimulates receptor dimerization, autophosphorylation of EGFR, activation of the receptor's internal, cytoplasmic tyrosine kinase domain, and initiation of multiple signal transduction and transactivation pathways involved in regulation of DNA synthesis and cell division. Accordingly, an EGFR antagonist is any substance that inhibits and/or disrupts one or more of these activities normally associated with EGFR stimulation.

Examples of EGFR antagonists include, for example, biological molecules, such as antibodies specific for EGFR, and small molecules that inhibit EGFR. (Specification p. 7, ll. 20-23, p. 8, ll. 3-4.) Aside from the many EGFR antagonists already known in the art, one skilled would be able to determine, using assays described, for example, in the specification at page 7, lines 14-19, whether or not new substances function as EGFR antagonists.

A known biological molecule EGFR antagonist is ERBITUXTM (IMC-C225), which is a chimeric (human/mouse) monoclonal antibody specific for EGFR. (Specification p. 12, line 12 – p. 14, line 9.) The monoclonal antibody ERBITUXTM specifically binds EGFR and blocks binding of a ligand, e.g., EGF. In addition, or alternatively, the monoclonal antibody ERBITUXTM may promote internalization of the receptor-antibody complex, preventing further stimulation of the receptor by its ligand or any other mechanism.

Another example of a biological molecule EGFR antagonist is ABX-EGF, which is a fully human IgG₂ monoclonal antibody specific for EGFR. ABX-EGF binds EGFR with high specificity, blocking binding of EGFR to both of its ligands, EGF and TGF- α . See, e.g., Figlin et al., Abstract 1102 presented at the 37th Annual Meeting of ASCO, San Francisco, CA, 12-15 May 2001. The sequence and characterization of ABX-EGF, which was formerly

known as clone E7.6.3,¹ is disclosed in U.S. Patent No. 6,235,883 (Abgenix, Inc.) at col. 28, line 62 through col. 29, line 36; Fig. 29-34.

One example of a small molecule EGFR antagonist is IRESSATM (ZD1939), which is a quinoxaline derivative that functions as an ATP-mimetic to inhibit EGFR. *See* U.S. Patent No. 5,616,582 (Zeneca Limited); WO 96/33980 (Zeneca Limited) at p. 4; *see also*, Rowinsky et al., Abstract 5 presented at the 37th Annual Meeting of ASCO, San Francisco, CA, 12-15 May 2001; Anido et al., Abstract 1712 presented at the 37th Annual Meeting of ASCO, San Francisco, CA, 12-15 May 2001.

TARCEVATM is another example of a small molecule EGFR antagonist. TARCEVATM (OSI-774) is a 4-(substitutedphenylamino)quinoxaline derivative [6,7-Bis(2-methoxy-ethoxy)-quinazolin-4-yl]- (3-ethynyl-phenyl)amine hydrochloride] EGFR inhibitor, which is described in WO 96/30347 (Pfizer Inc.) at, for example, page 2, line 12 through page 4, line 34 and page 19, lines 14-17. *See also* Moyer et al., *Cancer Res.*, 57: 4838-48 (1997); Pollack et al., *J. Pharmacol.*, 291: 739-48 (1999). TARCEVATM may function by inhibiting phosphorylation of EGFR and its downstream PI3/Akt and MAP (mitogen activated protein) kinase signal transduction pathways resulting in p27-mediated cell-cycle arrest. *See* Hidalgo et al., Abstract 281 presented at the 37th Annual Meeting of ASCO, San Francisco, CA, 12-15 May 2001.

Many other small molecules are known to inhibit EGFR. Some examples of small molecule EGFR antagonists are described in the specification at page 14, line 24 through page 16, line 7 and in WO 97/30034 (Zeneca Limited), WO 97/42187 (Zeneca Limited), and WO 98/33798 (Warner Lambert Company). Examples of specific small molecule EGFR

¹ See Yang et al., *Critical Rev. Oncol./Hematol.*, 38(1): 17-23, 2001.

antagonists include CI-1033, which is a quinoxaline (N-[4-(3-chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide) inhibitor of tyrosine kinases, particularly EGFR and is described in WO 00/31048 (Warner-Lambert Company) at page 8, lines 22-6; PKI166, which is a pyrrolopyrimidine inhibitor of EGFR and is described in WO 97/27199 (Novartis AG) at pages 10-12; GW2016, which is an inhibitor of EGFR and HER2; and ExB569.

EGFR antagonists have been shown to be effective when administered in combination with an antineoplastic agent to treat refractory tumors. For example, the monoclonal antibody ERBITUXTM has been shown to be effective in a phase II trial for administration in combination with Irinotecan (CPT-11) for the inhibition of refractory colorectal cancer (CRC). (Specification p. 23-24.) *See also* Saltz et al., Abstract 7 presented at the 37th Annual Meeting of ASCO, San Francisco, CA, 12-15 May 2001. Furthermore, the monoclonal antibody ERBITUXTM has been shown to inhibit refractory head and neck squamous cell carcinoma when administered in combination with an antineoplastic agent, i.e., cisplatin. (Specification p. 21-22.)

Thus, this rejection is moot and should be withdrawn.

Obviousness Issues

Claims 1-3, 6-9, and 22-23 were rejected under 35 U.S.C. § 103(a) as obvious over Baselga et al. In addition, claims 1-9 and 22-33 were rejected under 35 U.S.C. § 103(a) as obvious over Baselga et al. in light of Han et al. Finally, claims 1-3 and 6-33 were rejected under 35 U.S.C. § 103(a) as obvious over Baselga et al. in light of Amagase et al. According to the Office, Baselga et al. teaches a method of inhibiting tumor growth in humans with an

effective amount of a monoclonal antibody that inhibits EGFR phosphorylation, including combination therapy with a chemotherapeutic agent.

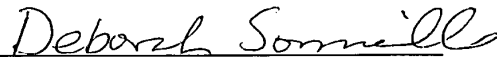
The new claims recite that the refractory tumors encompassed by the present invention have failed or been resistant to treatment. As discussed during the Examiner Interview, and set forth the Interview Summary, these new claims further defining the term refractory obviate the obviousness rejections and, as such, the rejections should be withdrawn.

CONCLUSION

Applicants believe that the present application is in condition for allowance, and respectfully request that the Office pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

The Office is authorized to charge any fees that may be necessary for consideration of this paper to Kenyon & Kenyon Deposit Account No. 11-0600.

Respectfully submitted,



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In the Specification:

At page 7, ll. 7-11:

The growth of refractory tumors is sufficiently inhibited in the patient to prevent or reduce the progression of the cancer (i.e. growth, invasiveness, metastasis, and/or recurrence). The EGFR antagonists of the present invention can be cytostatic or inhibit the growth of the refractory tumor. Preferably, the EGFR [ERGR] antagonist is cytolytic or destroys the tumor.

At page 7, ll. 20-25:

EGFR/HER1 antagonists include biological molecules and [or] small molecules. Biological molecules include all lipids and polymers of monosaccharides, amino acids and nucleotides having a molecular weight greater than 450. Thus, biological molecules include, for example, oligosaccharides and polysaccharides; oligopeptides, polypeptides, and proteins; and oligonucleotides and polynucleotides. Oligonucleotides and polynucleotides include, for example, DNA and RNA.

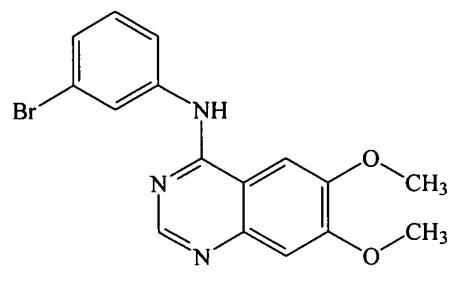
At page 14, ll. 19-23:

It is emphasized that small molecules can have any molecular weight. They are merely called small molecules because they typically have molecular weights less than 450. Small molecules include compounds that are found in nature as well as synthetic compounds.

The [Preferably, the] small molecules of the present invention inhibit the growth of refractory tumor cells that express EGFR/HER1 tyrosine kinase.

At page 15, lines 14-16

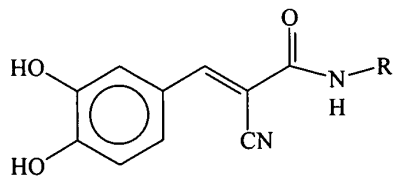
Fry et al., Science 265, 1093-1095 (1994) discloses a compound, PD 153035, having a structure that inhibits EGFR. The structure of PD 153035 is shown below: [in Figure 1. The compound shown in Figure 1 of the Fry et al. article is incorporated herein by reference.]



PD 153035

At page 15, lines 17-19

Osherov et al., J. Biol. Chem., 268, 11,134-142 (1993), disclose tyrphostins that inhibit EGFR/HER1 and HER2. The benzylidene malononitrile or tyrphostin compounds disclosed in the Osherov et al. article, and, in particular, those in Tables I, II, III, and IV are incorporated herein by reference and are set forth generically in the following structure:



wherein R is a cyclohexane, benzene, or benzene alkyl having 1-4 carbons in the alkyl, which benzene can be optionally substituted with Cl, OH, or CH₃.

In the Abstract:

A method of inhibiting the growth of refractory tumors that has failed or been resistant to treatment [are stimulated by a ligand of epidermal growth factor in human patients,] comprising administering to a [treating the] human [patients with an effective amount of] an epidermal growth factory receptor (EGFR) antagonist and an antineoplastic agent, such as a chemotherapeutic agent or radiation, wherein administration is effective to inhibit growth of the refractory tumor.